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博 士 学 位 论 文

RXRα影响(R)-Flurbiprofen对Aβ的调节

RXRα mediates (R)-flurbiprofen's effect on the levels of Aβ

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摘 要

阿尔茨海默病(AD)是以细胞内神经原纤维缠结（neurofibrillary tangle，NFT）和细胞外老年斑（senile plaque，SP）为主要病理特征的疾病。其中老年斑的主要成分是淀粉样蛋白（Aβ）。流行病学调查显示长期使用非甾体抗炎药（NSAIDs）能有效控制AD病情的发展。作为NSAIDs成员flurbiprofen的R型复合物，(R)-flurbiprofen能显著降低老年转基因AD小鼠脑中Aβ的沉积，且该药物具有安全性强的特点，从而成为倍受关注的治疗AD前景药物。然而，临床Ⅲ期的试验显示，(R)-flurbiprofen对AD病人认知能力的改善不如预期显著，Myriad Genetics公司的试验数据表明(R)-flurbiprofen对AD患者没有任何帮助。由于已知(R)-flurbiprofen能降低细胞外Aβ的沉积，但其对细胞内Aβ的影响却鲜为人知，而细胞内Aβ的增加也会引发神经细胞毒性。在这项研究中，我们以N2a695细胞（过量表达APP695的小鼠神经纤维瘤细胞N2a）为研究对象，检测(R)-flurbiprofen作用后细胞内外Aβ量的改变。结果显示，(R)-flurbiprofen在调节细胞外分泌性Aβ（包括40，42和38形式）下降的同时可使细胞内Aβ的水平上升。有资料表明，部分作为治疗AD备选药物的NSAIDs与核受体NR之间存在着不可分割的联系。由于NSAIDs 成员R-etodolac能特异性地与RXRα结合并抑制RXRα同二聚体转录活性。我们猜测RXR可能参与 (R)-flurbiprofen对A分泌的调节。我们的实验数据显示RXRα表达量的改变直接影响Aβ的生成，而且抑制RXRα的表达可使 (R)-flurbiprofen对A分泌的调节功能几乎完全丧失。此外，我们还发现在N2awt细胞中，当APP表达过量时， RXRα在细胞质中的分布比例明显增加，而在细胞核中则减少；与此相对应，与正常组比较，AD病人脑组织切片中RXRα在细胞质中的分布比例也呈增加趋势。总之，我们的结果表明（1）(R)-flurbiprofen在降低分泌性Ab的同时增高细胞内Ab的水平，这为(R)-flurbiprofen临床试验的失败提供了一个可能的解释；（2）RXRα能够直接影响Ab的产生，并参与(R)-flurbiprofen对Ab的调控，这为发现新型以核受体RXRα为靶点的治疗痴呆性疾病药物提出了新的方向；（3）APP/Ab可影响RXRα在细胞核和细胞质中的分布比例，提示Ab的细胞毒性也有可能通过影响RXRα来进行。

关键词：阿尔茨海默病; APP; A; RXRα; (R)-flurbiprofen

Abstract

Alzheimer's disease (AD) is characterized by extracellular neuritic plaques composed of fibrillar β-amyloid (Aβ) peptide and intracellular neurofibrillary tangles (NFTs). Multiple lines of evidence suggest that overproduction/aggregation of A in the brain is the major cause of AD pathogenesis. Epidemiological studies indicate that long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with a reduced risk of AD development. (R)-flurbiprofen, the R-enantiomer of flurbiprofen racemate, has been found effective in reducing amyloid pathology in AD transgenic mouse models and become a prospective candidate for AD treatment. Unfortunately, the results from phase clinical trials using (R)-flurbiprofen for AD treatment by Myrial Genetics were disappointing. Thus, it is necessary to determine the mechanism by which (R)-flurbiprofen exerts its anti-AD effects. In this study, we examined the effect of (R)-flurbiprofen on expression of Aβ in N2a695 cells (a mouse neuroblastoma cell line which overexpresses APP695). Our results showed that (R)-flurbiprofen treatment reduced the levels of extracellular Aβ (including Aβ 40, Aβ 42, and Aβ38), consistent with previous reports. Surprisingly, we found that (R)-flurbiprofen treatment significantly increased the levels of intracellular A, which has been suggested to be more correlated with AD than extracellular A. Retinoid X receptor (RXR) is a member of the nuclear receptor superfamily, which can mediate the anti-tumor effects. In this study, we found that downregulation of RXR by siRNA significantly increased the level of extracellular A but had no effect on intracellular A. Moreover, The inhibitory effect of (R)-flurbiprofen on extracellular A was abolished upon downregulation of RXR. In addition, when APP was overexpressed in wild type N2a cells, there was a re-distribution of RXRα from the nucleus to the cytoplasm. Correspondingly, the distribution of

RXRα in the cytoplasm of AD patient brain cells was dramatically increased. Together, our results demonstrate that (1) (R)-flurbiprofen reduces Ab secretion but increases the levels of intracellular Ab, providing a possible explanation for the failure of clinical trials of (R)-flurbiprofen for AD treatment; (2) RXR regulates A secretion and is involved in (R)-flurbiprofen-mediated Ab generation, suggesting that RXR might be a potential target for AD drug development; and (3) APP/Aβaffects the distribution of RXRin cytoplasm and nucleus.

Keywords: Alzheimer's disease; APP; A; (R)-flurbiprofen; retinoid X receptor  .

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